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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,462	05/01/2001	Jehad Charo	1430-264	7394

7590 03/11/2003

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,462	CHARO ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *14-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-24 are pending in the application. Claims 14-23 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-13 and 24 are currently under examination.

This Office Action is in response to the Amendment filed on 12/16/02.

Response to Amendment

The rejection of claims 2-6 and 11 under 35 U.S.C.112 second paragraph has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 1-4, 7-13 and 24 under 35 U.S.C.103(a) is maintained for same reason set forth of the record mailed on 7/16/02 and further discussed below.

Claims 5 and 6 are rejected under 35 U.S.C.103(a) for reasons discussed below.

Response to Arguments

Election/Restrictions

Applicants dispute the statement on page 3 of the previous office action (if Applicants regard each compound can constitute a distinct invention from the other, the unity of the invention would have been broken). Applicants argue that the PCT Article and Rules only require that a "special technical feature" be shared by the claims for them to be examined in the same application, and the claims can be separately patentable without breaking unity of invention.

The Examiner wants to clarify that according to PCT rule 13.1, inventions which are not so linked as form a single general inventive concept are deemed lack of unity. A "special technical feature must" be shared by the claimed inventions to for a single general inventive

concept. In the statement that is disputed above, the Examiner merely try to point out if each of the compound recited in the claim 1 can constitute a distinct invention from each other, then they do not share a "special technical feature", thus they would lack unity of invention. In that case, they would be examined separately. However, since Applicants do not regard each compound as distinct invention, all of these compounds are under examination currently.

Claim Rejections - 35 USC § 103

In response to the rejection of claims 1-4, 7-13 and 24, Applicants argue that the mechanism for tucaresol's action as an adjuvant in conventional protein vaccine and DNA vaccine is different. Applicants assert that there were good reasons to have believed that tucaresol would not work in the setting of a DNA vaccine, hence, there is no expectation of success. Applicants state that the immune responses elicited by protein vaccine (both viral and non-viral micro-organisms) utilizes mechanism illustrated by either pathway A or B (attached figure), whereas immune responses elicited by DNA vaccine utilize a unique mechanism of antigen handling that involves neither A or B. Applicants regard the major difference between the two is that the wild type infection involves an array of danger signals and co-stimulatory signals initiated by pathogen associated molecular patterns during the uptake/entry phase to APC which is not presented in DNA vaccine. Applicants assert that adjuvants and tucaresol work on co-stimulatory mechanisms and do not affect the recognition of antigen by the T cell receptor or the signal it transduces. Applicants further assert that the co-stimulatory environment associated with DNA vaccination is different from the one associate with conventional protein vaccine, hence tucaresol is only effective in pathway A and B, but not in DNA vaccine. Applicants also indicate the surprising feature of the invention is the demonstration of a TH2 response instead of

TH1 response as reported earlier. Applicants further argue that Examiner's interpretation of the Rhodes is not based on the reference's disclosure but uses hindsight gained from Applicants teaching of the efficacy of tucaresol in DNA vaccination. Applicants reiterate their comments that known immuno-potentiating agents such as GM-CSF have been tried with DNA vaccination with limited success, whereas conventional adjuvants such as alum are not effective with DNA vaccination. Applicants further argue that Herrman et al. do not disclose particular adjuvants which might expected to work in DNA vaccination. Therefore, Applicants conclude that the combination of Rhode and Herrman references do not suggest a reasonable expectation of success to use tucaresol as adjuvant in DNA vaccination.

Applicants' argument has been fully considered but deemed not persuasive. The Examiner acknowledges that not every known immuno-potentiating agents that functions in protein vaccination would be effective in DNA vaccination, however, there is sufficient teaching to support that there is a reasonable expectation of success that tucaresol would potentiate immune response with DNA vaccination. As discussed previously, Rhodes et al. teach that the mechanism by which the Schiff base-forming compounds (including tucaresol) influence immune responses is by reacting with amino groups on the surface of lymphocytes and antigen presenting cells, thereby provide co-stimulation to T-cells, amplifying the co-stimulation provided by physiological Schiff base-formation between ligands on the surface of cells (see col.16, lines 49-56). In addition, reference 10 cited by Applicants (Rhodes et al 1995) teaches that convergence of Schiff base signaling with TCR signaling has been identified at the level of tyrosyl phosphorylation of the MAP-kinase ERK2 (see page 73, bottom of 1st col. through top of 2nd col). Therefore, tucaresol provide immuno-potentiating response by direct engaging T cells

and providing signals that converges with signal 1 result from TCR-antigen ligation. This signal 1 is considered same for natural infection, conventional vaccines and DNA vaccines (see Figure D, legend).

Applicants assert that Figure C represents the delivery of antigen as DNA that differs from pathway A and B in which the antigen is either taken up by viral receptor or endocytosis. However, protein antigen encoded by DNA can also be secreted from the cell (the claims have no limitation on what cell type the DNA is introduced) and subsequently taken up by antigen presenting cells, and produce a MHC class II response which resembles the pathway illustrated in Figure B. Therefore, by forming Schiff base directly with CD4+ T cell, thus amplifying co-stimulatory effects provided by physiological Schiff base formation between ligands on the surface of the cells, there is reasonable expectation that tucaresol would enhance immune response elicited by the antigen.

The Examiner acknowledges that Applicants have demonstrated that co-administration of tucaresol and DNA encoding HSP-65 elicits TH2 mediated antibody response in addition to previously reported TH1 response. However, this finding is not a limitation in the presently claimed invention.

It would have been obvious to use Schiff base forming compound such as tucaresol to enhance immune response to DNA vaccination because of the combination teaching of Rhodes et al and Herrman et al. as discussed in the two previous office action. Rhodes et al. has demonstrated that tucaresol increased T-lymphocyte priming to antigen and increased antibody production (see Figure 1-7). This is entirely disclosed by Rhodes et al., not by hindsight reasoning from Applicants' disclosure. Rhodes et al. teach that these compound can be used as a

vaccine adjuvant (see col. 9, lines 38-40). This notion is also reiterated in reference 10 cited by Applicants (Rhodes 1995, page 73, top left). Therefore, Applicants does not provide sufficient evidence that tucaresol would not function as a vaccine adjuvant in the setting of DNA vaccination. As such, the claimed invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

New Grounds of Rejection

Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhodes et al., in view of Herrman et al.

Rhodes (US 5,508,310) teaches tucaresol, a member of Schiff base compound, can be used as vaccine adjuvant, and a vaccine can be prepared by formulating the antigenic component with tucaresol and administered simultaneously (see col.9, 38-40). Rhodes further discloses that the compound can be administered by oral, parenteral and inhalation at a dose range from 0.5 to 50mg/kg per day (see column 9, 7^{th}-9^{th} paragraph). Rhodes further teaches that the administration of the compound may be repeated (col.14, lines 15-30). Rhodes further teaches that the mechanism by which Schiff base forming compounds influence immune responses is the same in that compounds react with amino groups on the surface of lymphocytes and antigen presenting cells, therefore providing co-stimulation to T cells, amplifying the co-stimulation provided by physiological Schiff base-formation between ligands on the surface of cells. Rhodes further teaches that low and medium concentration of Schiff base compound will enhance immune responses whereas high concentrations will be inhibitory (see column 16, last

paragraph). However, Rhodes et al. does not teach that tucaresol can be used with DNA vaccination.

Herrmann et al. (US 5,620,896) teaches a method of immunizing mammals against rotavirus infections by injecting a vector comprising DNA encoding antigenic peptide to the mammals in the presence of adjuvants (see column (column 7, 2nd–4th paragraph).

Combining the teaching of Rhodes and Herrmann et al., it would have been obvious to one of ordinary skill in the art to practice the method of vaccinating a mammal by administering a nucleotide encoding an antigenic peptide, and augmenting immune response of said vaccine by using Schiff base compound as adjuvant. The ordinary artisan would have been motivated to use Schiff base compound as a vaccine adjuvant because of the teaching of Rhodes, who not only teach those compounds can stimulate immune response but also provides the mechanism of such stimulation. The ordinary artisan would have a reasonable expectation of success because of the teaching of Herrmann et al., who teach a method of vaccinating a mammal by administering a vector comprising DNA encoding an antigenic peptide, and the teaching of Rhodes, who teach that Schiff base compound can potentiate immune response to an antigenic peptide as well as the mechanism of its function. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention is made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
March 4, 2003

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER